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FOR

ELECTRODE ASSEMBLY FOR NERVE CONTROL

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ELECTRODE ASSEMBLY FOR NERVE CONTROL

CROSS-REFERENCES TO RELATED APPLICATIONS

The present patent application is a continuation-in-part of US Patent Application 10/205,474, filed July 24, 2002, entitled, "Electrode assembly for nerve control," which (a) claims the benefit of US Provisional Patent Application 60/383,157 to Ayal et al., filed May 23, 2002, entitled, "Inverse recruitment for autonomic nerve systems," and (b) is a continuation-in-part of PCT Patent Application PCT / IL02 / 00068, filed January 23, 2002, entitled, "Treatment of disorders by unidirectional nerve stimulation," which is a continuation-in-part of US Patent Application 09/944,913, filed August 31, 2001, entitled, "Treatment of disorders by unidirectional nerve stimulation." The '068 application, the '913 application, the '474 application, and the '157 applications are assigned to the assignee of the present patent application and are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates generally to electrical stimulation of tissue, and specifically to methods and devices for regulating the stimulation of nerves.

BACKGROUND OF THE INVENTION

As defined by Rattay, in the article, "Analysis of models for extracellular fiber stimulation," IEEE Transactions on Biomedical Engineering, Vol. 36, no. 2, p. 676, 1989, which is incorporated herein by reference, the activation function (AF) is the second spatial derivative of the electric potential along an axon. In the region where the activation function is positive, the axon depolarizes, and in the region where the activation function is negative, the axon hyperpolarizes. If the activation function is sufficiently positive, then the depolarization will cause the axon to generate an action potential; similarly, if the activation function is sufficiently negative, then local blocking of action potentials transmission occurs. The activation function depends on the current applied, as well as the geometry of the electrodes and of the axon.

For a given electrode geometry, the equation governing the electrical potential is:

$$\nabla(\acute{o}\nabla U) = 4\partial j,$$

where U is the potential, ó is the conductance tensor specifying the conductance of the various materials (electrode housing, axon, intracellular fluid, etc.), and j is a scalar function representing the current source density specifying the locations of current injection. The activation function is found by solving this partial differential equation for U. If the axon is defined to lie in the z direction, then the activation function is:

$$AF = \frac{\partial^2 U}{\partial z^2} .$$

In a simple, illustrative example of a point electrode located a distance d from the axis of an axon in a uniformly-conducting medium with conductance ó, the two equations above are solvable analytically, to yield:

$$AF = \frac{I_{el}}{4\partial\acute{o}} \cdot \frac{2z^2 - d^2}{\left(z^2 + d^2\right)^{2.5}} ,$$

where I_{el} is the electrode current. It is seen that when ó and d are held constant, and for a constant positive I_{el} (to correspond to anodal current), the minimum value of the activation function is negative, and is attained at z = 0, i.e., at the point on the nerve closest to the source of the anodal current. Thus, the most negative point on the activation function corresponds to the place on a nerve where hyperpolarization is maximized, namely at the point on the nerve closest to the anode.

Additionally, this equation predicts positive "lobes" for the activation function on either side of z = 0, these positive lobes peaking in their values at a distance which is dependent on each of the other parameters in the equation. The positive values of the activation function correspond to areas of depolarization, a phenomenon typically associated with cathodic current, not anodal current.

However, it has been shown that excess anodal current does indeed cause the generation of action potentials adjacent to the point on a nerve corresponding to z = 0, and this phenomenon is therefore called the "virtual cathode effect." (An analogous, but reverse phenomenon, the "virtual anode effect" exists responsive to excess cathodic stimulation.)

US Patent 6,230,061 to Hartung, which is incorporated herein by reference, describes an electrode arrangement for stimulating the heart by means of: (a) an implantable cardiac pacemaker, (b) a first electrode, coupled to a first output of the pacemaker via an intracardiac electrode line, and (c) a second electrode, for transmitting electrical stimulation pulses to the heart tissue, coupled to a second output of the pacemaker via the electrode line. The voltage pulses at the two electrodes have differing polarities relative to a third electrode. The first and second electrodes are arranged on the electrode line in such a way that the electrical dipole field which forms is distorted towards the stimulation point in such a way that a raised gradient above the stimulus threshold is formed there.

A number of patents and articles describe methods and devices for stimulating nerves to achieve a desired effect. Often these techniques include a design for an electrode or electrode cuff.

US Patents 4,608,985 to Crish et al. and 4,649,936 to Ungar et al., which are incorporated herein by reference, describe electrode cuffs for selectively blocking orthodromic action potentials passing along a nerve trunk, in a manner intended to avoid causing nerve damage.

PCT Patent Publication WO 01/10375 to Felsen et al., which is incorporated herein by reference, describes apparatus for modifying the electrical behavior of nervous tissue. Electrical energy is applied with an electrode to a nerve in order to selectively inhibit propagation of an action potential.

US Patent 5,755,750 to Petruska et al., which is incorporated herein by reference, describes techniques for selectively blocking different size fibers of a nerve by applying direct electric current between an anode and a cathode that is larger than the anode.

US Patent 5,487,756 to Kallesoe et al., which is incorporated herein by reference, describes an implantable cuff having a closure comprising a set of small interdigitated tubes lying along the edges of a longitudinal slit opening in the cuff. A rod-like locking member is inserted through the interdigitated tubes to lock the cuff closed. A flexible flap attached to the inside of the cuff is described as electrically and mechanically isolating the interior of the cuff from the exterior.

US Patent 5,824,027 Hoffer et al., which is incorporated herein by reference, describes a nerve cuff having one or more sets of electrodes for selectively recording electrical activity in a nerve or for selectively stimulating regions of the nerve. Each set of electrodes is located in a longitudinally extending chamber between a pair of longitudinal ridges which project into the bore of the nerve cuff. The ridges are electrically insulating and serve to improve the selectivity of the nerve cuff. The ridges seal against an outer surface of the nerve without penetrating the nerve.

The following articles, which are incorporated herein by reference, may be of interest:

Ungar IJ et al., "Generation of unidirectionally propagating action potentials using a monopolar electrode cuff," Annals of Biomedical Engineering, 14:437-450 (1986)

Sweeney JD et al., "An asymmetric two electrode cuff for generation of unidirectionally propagated action potentials," IEEE Transactions on Biomedical Engineering, vol. BME-33(6) (1986)

Sweeney JD et al., "A nerve cuff technique for selective excitation of peripheral nerve trunk regions," IEEE Transactions on Biomedical Engineering, 37(7) (1990)

Naples GG et al., "A spiral nerve cuff electrode for peripheral nerve stimulation," by IEEE Transactions on Biomedical Engineering, 35(11) (1988)

van den Honert C et al., "Generation of unidirectionally propagated action potentials in a peripheral nerve by brief stimuli," Science, 206:1311-1312 (1979)

van den Honert C et al., "A technique for collision block of peripheral nerve: Single stimulus analysis," MP-11, IEEE Trans. Biomed. Eng. 28:373-378 (1981)

van den Honert C et al., "A technique for collision block of peripheral nerve: Frequency dependence," MP-12, IEEE Trans. Biomed. Eng. 28:379-382 (1981)

Rijkhoff NJ et al., "Acute animal studies on the use of anodal block to reduce urethral resistance in sacral root stimulation," IEEE Transactions on Rehabilitation Engineering, 2(2):92 (1994)

Mushahwar VK et al., "Muscle recruitment through electrical stimulation of the lumbo-sacral spinal cord," IEEE Trans Rehabil Eng, 8(1):22-9 (2000)

Deurloo KE et al., "Transverse tripolar stimulation of peripheral nerve: a modelling study of spatial selectivity," Med Biol Eng Comput, 36(1):66-74 (1998)

Tarver WB et al., "Clinical experience with a helical bipolar stimulating lead," Pace, Vol. 15, October, Part II (1992)

Hoffer JA et al., "How to use nerve cuffs to stimulate, record or modulate neural activity," in *Neural Prostheses for Restoration of Sensory and Motor Function*, Chapin JK et al. (Eds.), CRC Press (1st edition, 2000)

In physiological muscle contraction, nerve fibers are recruited in the order of increasing size, from smaller-diameter fibers to progressively larger-diameter fibers. In contrast, artificial electrical stimulation of nerves using standard techniques recruits fibers in a larger- to smaller-diameter order, because larger-diameter fibers have a lower excitation threshold. This unnatural recruitment order causes muscle fatigue and poor force gradation. Techniques have been explored to mimic the natural order of recruitment when performing artificial stimulation of nerves to stimulate muscles.

Fitzpatrick et al., in "A nerve cuff design for the selective activation and blocking of myelinated nerve fibers," Ann. Conf. of the IEEE Eng. in Medicine and Biology Soc, 13(2), 906 (1991), which is incorporated herein by reference,

describe a tripolar electrode used for muscle control. The electrode includes a central cathode flanked on its opposite sides by two anodes. The central cathode generates action potentials in the motor nerve fiber by cathodic stimulation. One of the anodes produces a complete anodal block in one direction so that the action potential produced by the cathode is unidirectional. The other anode produces a selective anodal block to permit passage of the action potential in the opposite direction through selected motor nerve fibers to produce the desired muscle stimulation or suppression.

The following articles, which are incorporated herein by reference, may be of interest:

Rijkhoff NJ et al., "Orderly recruitment of motoneurons in an acute rabbit model," Ann. Conf. of the IEEE Eng., Medicine and Biology Soc., 20(5):2564 (1998)

Rijkhoff NJ et al., "Selective stimulation of small diameter nerve fibers in a mixed bundle," Proceedings of the Annual Project Meeting Sensations/Neuros and Mid-Term Review Meeting on the TMR-Network Neuros, April 21-23, 1999, pp. 20-21 (1999)

Baratta R et al., "Orderly stimulation of skeletal muscle motor units with tripolar nerve cuff electrode," IEEE Transactions on Biomedical Engineering, 36(8):836-43 (1989)

The following articles, which are incorporated herein by reference, describe techniques using point electrodes to selectively excite peripheral nerve fibers distant from an electrode without exciting nerve fibers close to the electrode:

Grill WM et al., "Inversion of the current-distance relationship by transient depolarization," IEEE Trans Biomed Eng, 44(1):1-9 (1997)

Goodall EV et al., "Position-selective activation of peripheral nerve fibers with a cuff electrode," IEEE Trans Biomed Eng, 43(8):851-6 (1996)

Veraart C et al., "Selective control of muscle activation with a multipolar nerve cuff electrode," IEEE Trans Biomed Eng, 40(7):640-53 (1993)

SUMMARY OF THE INVENTION

It is an object of some aspects of the present invention to provide improved apparatus and methods for stimulating a nerve.

It is a further object of some aspects of the present invention to provide improved methods and apparatus for configuring an electrode assembly.

It is still a further object of some aspects of the present invention to provide improved methods and apparatus for driving an electrode assembly to apply current to a nerve.

It is an additional object of some aspects of the present invention to provide improved methods and apparatus for coupling a cuff to longitudinal tissue, such as a nerve.

In preferred embodiments of the present invention, an electrode assembly for applying current to a nerve comprises a cathode, a primary inhibiting anode and a secondary inhibiting anode, which are fixed within a housing. The cathode, near one end of the housing, is placed on or near the nerve, over a "cathodic longitudinal site" of the nerve, and is driven by a control unit to apply a cathodic current to the nerve. The primary inhibiting anode, adjacent to the cathode in the housing, is placed on or over a "primary anodal longitudinal site" of the nerve, and is driven to apply a primary anodal current to the nerve. The secondary inhibiting anode, which is separated from the cathode by the primary inhibiting anode, is placed on or over a "secondary anodal longitudinal site" of the nerve, and applies a secondary anodal current to the nerve.

Typically, the cathodic current applied at the cathodic longitudinal site stimulates fibers within the nerve to generate action potentials which travel in both directions within the nerve -- i.e., towards the anodes ("the anodal direction"), and in the opposite direction, out of the housing, towards a target ("the target direction"). The anodal current, by contrast, is typically applied so as to inhibit the action potentials which were generated at the cathodic longitudinal site and which subsequently traveled in the anodal direction.

For most applications, the secondary anodal current is of lower magnitude than the primary anodal current. In this manner, the "virtual cathode" effect induced by the primary anodal current is minimized. As described in the Background section of the present patent application, the virtual cathode effect can stimulate --rather than block-- the generation of action potentials in fibers in a region adjacent to the application of anodal current of a sufficiently high magnitude. In accordance with a preferred embodiment of the present invention, application of the primary and secondary anodal currents in appropriate ratios is configured to generally minimize the virtual cathode effect. Typically, but not necessarily, the ratio of the primary to the secondary anodal current ranges from 5:1 to 10:1.

In a preferred embodiment, a tertiary inhibiting anode is employed to reduce any virtual cathode effect which may be induced by the secondary inhibiting anode. For example, relative to a normalized cathodic current of -1, the primary inhibiting anode, secondary inhibiting anode, and tertiary inhibiting anode may be configured to apply respective currents of 0.66, 0.25, and 0.09. For some applications, the various anodes are independently driven by a control unit, so as to optimize the minimization of the virtual cathode effect and the maximization (when appropriate) of the anodally-induced hyperpolarization. Alternatively, fixed ratios are pre-defined for the currents applied by the anodes, and are set in hardware, e.g., by a set of resistors which link a single lead coming from the control unit to the respective anodes.

In a preferred embodiment, an elongated anode replaces the anodes described hereinabove. The elongated anode, when placed on or over a nerve, preferably has at least two levels of electrical impedance associated therewith, between respective sites on the elongated anode and the nerve. Most preferably, the portion of the elongated anode nearest the cathode has a lower level of impedance to the nerve than does another portion of the elongated anode, further from the cathode. For some applications, the variation in impedance is achieved by applying a coating (e.g., IrO2 or a more resistive material) in progressively increasing thickness to the elongated anode, beginning with a low level of the

coating at the end of the elongated anode near the cathode. Alternatively or additionally, the geometry of the elongated anode is configured so as to effect the change in impedance as described. It is noted that the impedance between any site on the elongated anode and the nerve is a function not only of the properties of the anode itself, but also of the biological material which naturally permeates the region between the nerve and the anode.

For some applications, a primary fiber-selection anode is incorporated into the housing, adjacent to the cathode and on the other side of the housing from the primary and secondary inhibiting anodes. (Thus, the sequence of electrodes in the housing is: primary fiber-selection anode, cathode, primary inhibiting anode, secondary inhibiting anode.) The primary fiber-selection anode is preferably driven to apply anodal current of sufficient magnitude to block cathode-induced action potential propagation in some fibers, generally the larger fibers, which are more sensitive to the anodal current. If the current applied by the primary fiber-selection anode is not too high, then less-sensitive fibers, typically the smaller fibers in the nerve, are not blocked by the anodal current. Therefore, action potentials induced by the cathode continue to propagate in the smaller fibers, past the primary fiber-selection anode and out of the housing. By increasing the current driven through the primary fiber-selection anode, progressively smaller fibers are inhibited from propagating action potentials. Conversely, by decreasing the application of current through the primary fiber-selection anode, larger fibers are able to propagate action potentials, until, in the limit where the primary fiber-selection anode's current is zero, all fibers stimulated by the cathode convey their action potentials out of the housing and towards the target.

In a preferred embodiment, a secondary fiber-selection anode is also incorporated into the housing, adjacent to the primary fiber-selection anode and on the far side of the cathode. (Thus, the sequence of electrodes in the housing is: secondary fiber-selection anode, primary fiber-selection anode, cathode, primary inhibiting anode, secondary inhibiting anode.) In a fashion analogous to that described hereinabove with respect to the secondary inhibiting anode, the secondary fiber-selection anode is preferably driven to apply a current to the nerve

smaller than that applied by the primary fiber-selection anode, so as to counteract the virtual cathode effect which would otherwise, in some circumstances, induce action potential propagation responsive to the current applied by the primary fiber-selection anode.

In preferred embodiments of the present invention, an electrode assembly for applying current to a nerve having a longitudinal axis comprises a housing, adapted to be placed in a vicinity of the nerve and a cathode and an anode, fixed to the housing. The cathode and anode are attached to the housing such that, when the housing is placed in the vicinity of the nerve, both the distance of the cathode and the distance of the anode to the axis are at least approximately 1.5 times greater than the radius of the nerve. By placing the cathode and anode at such a distance, increased electrical field uniformity is obtained within the nerve. In particular, the activation function (as defined in the Background section of this application) varies only relatively little across the cross-section of the nerve. This, in turn, increases the ability of a control unit driving the cathode and anode to assure that most fibers within the nerve will experience generally the same level of applied currents.

In preferred embodiments of the present invention, an electrode assembly is provided for applying current to a nerve having a radius and a longitudinal central axis. The electrode assembly comprises a housing, which is placed in a vicinity of the nerve, and first and second electrodes, fixed to the housing. An insulating element is fixed to the housing between the first and second electrodes so as to define a characteristic closest "insulating element distance" to the central axis that is at least approximately 1.5 times greater than the radius of the nerve. Typically, the electrodes are located at the same distance from the central axis or at a greater distance therefrom. In a preferred embodiment, the face of each electrode is located at a distance from the central axis less than or equal to the closest insulating element distance plus the width (i.e., the longitudinal extent along the nerve) of the electrode. In a preferred embodiment, the width of each electrode is approximately one half of the radius of the nerve.

Although many geometrical configurations are suitable for applying the principles of the present invention, the housings, electrodes, and insulating elements described herein are typically generally cylindrical, i.e., having circular cross-sections. Alternatively or additionally, at least some of these components are located at discrete locations with respect to the axis of the nerve (e.g., a single electrode located at "12 o'clock," or four electrodes or insulating elements may be evenly distributed around the axis).

In preferred embodiments of the present invention, an electrode assembly for applying current to a nerve comprises a cathode and a plurality of anodes. The cathode is placed in a vicinity of a cathodic site of the nerve, and the plurality of anodes are placed in a vicinity of respective anodal longitudinal sites of the nerve. The plurality of anodes apply respective anodal currents to the nerve, that define, in combination, an anodal activation function having a depolarization portion and a hyperpolarization portion. For many applications of the present invention, the hyperpolarization portion is the "desired" portion of the anodal activation function. For example, the hyperpolarization portion may be configured to block action potential propagation in a particular direction.

By contrast, it is desired when performing many of these applications to minimize the depolarization portion of the anodal activation function, because the location on the nerve of the depolarization portion corresponds to the location of the virtual cathode described hereinabove. If no countermeasures would be taken, the virtual cathode could be associated with an undesired stimulation of fibers in the nerve under the virtual cathode. The virtual cathode effect could be minimized to some extent by reducing the anodal current, but, if in excess, this would result in a decrease in the magnitude of the (typically desired) hyperpolarization region. If the anodal current is only minimally reduced, in order to avoid adversely decreasing the magnitude of the hyperpolarization region, then the virtual cathode effect would typically still be present. The inventors have determined that for many electrode configurations, there is no suitable balance, i.e., either the virtual cathode effect will be reduced to a desired level, or the hyperpolarization portion of the activation function will be maintained at a sufficiently high magnitude.

To address this issue, the plurality of anodes provided by these embodiments of the present invention are preferably configured so as to have the maximum magnitude of the hyperpolarization portion be at least five times greater than the maximum magnitude of the depolarization amplitude. In this manner, the desired hyperpolarization effect is preserved, and the extent of depolarization due to the anodal current is minimized. Preferably, this ratio of anodally-induced hyperpolarization to depolarization is attained by using one or more of the following: (a) one or more secondary inhibiting anodes, as described hereinabove, to minimize the virtual cathode effect, (b) one or more insulating elements whose closest approach to the nerve generally remains further from the central axis of the nerve than approximately 1.5 times the radius of the nerve, or (c) electrodes, whose closest approach to the nerve generally remains further from the central axis of the nerve than approximately 1.5 times the radius of the nerve.

In preferred embodiments of the present invention, an electrode assembly for applying current to a nerve having a longitudinal axis, comprises two or more electrodes, adapted to be placed in a vicinity of a longitudinal site of the nerve, at respective positions around the axis. If there are only two electrodes, then the control unit preferably alternates the direction of driving a current between the two electrodes at a rate greater than 1000 Hz.

When there are three or more electrodes, thereby defining a ring of electrodes, the control unit preferably cycles around the electrodes in accordance with a stimulation protocol. For example, one such protocol for three electrodes may include driving current between electrodes 1 and 2, then 2 and 3, then 3 and 1, then 1 and 2, etc., cycling through the combinations at an electrode-pair transition average rate of greater than 1000 Hz, or, for some applications, greater than 10,000 Hz. For larger numbers of electrodes, e.g., 6, 12, or 24, the stimulation cycling protocol is typically more complex, and is preferably configured to cause current to pass through or close to most or all fibers in the nerve at the longitudinal site where the ring of electrodes is placed. One such complex protocol includes effectively creating a star out of the current lines passing through the nerve, or

ensuring that each electrode in the ring conveys current to some, most, or all of the other electrodes.

Advantageously, due to the very high application rate of the current from the different electrodes compared to the relatively-low biological response rate of the fibers within the nerve, the fibers at that longitudinal site are effectively all stimulated at substantially the same time. In this manner, a single wave of action potential propagation is initiated from the longitudinal site at substantially the same time, and can be subsequently manipulated at other sites on the nerve using techniques described herein or in one or more of the patent applications cited herein that are assigned to the assignee of the present patent application and are incorporated herein by reference. Further, unlike solid ring electrodes which surround the nerve and conduct a significant portion of their current outside of the nerve, directly to the anode or cathode adjacent thereto, a larger portion of the current is conveyed into the nerve itself using the stimulation protocols described herein. From the "perspective" of the nerve, which functions at rates considerably slower than the switching rate of the ring of electrodes, it is as if a large portion of its nerve fibers were simultaneously stimulated.

In preferred embodiments of the present invention, an electrode assembly for applying current to a nerve having a longitudinal axis comprises a ring of two or more cathodes and a ring of two or more anodes, each ring of electrodes adapted to be placed around the nerve axis, at a respective cathodic or anodal longitudinal site of the nerve. Preferably, a control unit drives an anode in the ring of anodes to drive current through the nerve to a cathode typically at another orientation with respect to the axis, in order to stimulate fibers in the nerve nearer the cathode. Thus, for example, if each ring has twelve electrodes, then in one preferred stimulation protocol, the anode at "12 o'clock" with respect to the axis drives current generally through the nerve to the cathode at 6 o'clock. After a very short delay (typically 10 - 100 microseconds), the anode at 1 o'clock drives current generally through the nerve to the cathode at 7 o'clock. The pattern is preferably continued for all of the electrodes. It will be appreciated by one who has read the disclosure of the present patent application that a variety of stimulation protocols

may be developed, and that a suitable protocol should typically be determined in accordance with the anatomy of the nerve, the types of nerve fibers therein, and the purpose of the stimulation, among other factors.

In some embodiments of the present invention, a tubular cuff for implantation around tubular tissue is shaped so as to define: (a) a longitudinal slit having a first edge and a second edge, and (b) one or more holes in a vicinity of the first edge. The cuff comprises one or more protrusions, which are coupled to the cuff in a vicinity of the second edge, and are adapted to hold the first and second edges together when the protrusions are passed through the holes.

For some applications, the tubular cuff comprises one or more filaments, such as sutures or filaments made from silicone, which are coupled to respective protrusions. For some applications, silicone sutures are an integral portion of a silicone cuff. In order to draw the protrusions through respective holes, a surgeon threads the filaments through the respective holes, and draws the filaments until the protrusions pass through the respective holes. Upon completion of the implantation, the surgeon may clip off the filaments. In embodiments of the cuff that do not comprise filaments, the surgeon typically uses standard surgical tools, such as tweezers, to draw the protrusions through the holes.

There is therefore provided, in accordance with a preferred embodiment of the present invention, apparatus for applying current to a nerve, including:

a cathode, adapted to be placed in a vicinity of a cathodic longitudinal site of the nerve and to apply a cathodic current to the nerve;

a primary inhibiting anode, adapted to be placed in a vicinity of a primary anodal longitudinal site of the nerve and to apply a primary anodal current to the nerve; and

a secondary inhibiting anode, adapted to be placed in a vicinity of a secondary anodal longitudinal site of the nerve and to apply a secondary anodal current to the nerve, the secondary anodal longitudinal site being closer to the primary anodal longitudinal site than to the cathodic longitudinal site.

In a preferred embodiment, the apparatus is adapted to be placed on the nerve such that, relative to the anodal longitudinal sites, the cathodic longitudinal site is proximal to a brain of a subject, the subject including the nerve. Alternatively, the apparatus is adapted to be placed on the nerve such that, relative to the anodal longitudinal sites, the cathodic longitudinal site is distal to a brain of a subject, the subject including the nerve.

In a preferred embodiment, the primary inhibiting anode is adapted to apply the primary anodal current to the nerve so as to block propagation of action potentials past the primary anodal longitudinal site.

For some applications, the primary inhibiting anode is adapted to apply the primary anodal current to the nerve so as to block propagation past the primary anodal longitudinal site of action potentials in a first set of nerve fibers, and to allow propagation past the primary anodal longitudinal site of action potentials in a second set of nerve fibers, the second set of nerve fibers having characteristic diameters generally smaller than characteristic diameters of the nerve fibers in the first set.

In a preferred embodiment, the cathode includes a plurality of cathodes, placed in the vicinity of the cathodic longitudinal site of the nerve, at respective positions around an axis of the nerve. In this case, the plurality of cathodes are preferably adapted to apply the cathodic current at a characteristic frequency greater than 1000 Hz.

Preferably, the apparatus includes a primary insulating element disposed between the cathode and the primary inhibiting anode. The primary insulating element is typically disposed in a position with respect to the cathode and the primary inhibiting anode so as to guide the flow of current between the cathode and the primary inhibiting anode. For some applications, the apparatus includes a secondary insulating element, disposed between the primary inhibiting anode and the secondary inhibiting anode. In this case, a characteristic size of the secondary insulating element is preferably smaller than a characteristic size of the primary insulating element. Alternatively or additionally, a characteristic distance of the

secondary insulating element to an axis of the nerve is greater than a characteristic distance of the primary insulating element to the axis of the nerve.

In some preferred embodiments, the apparatus includes a tertiary inhibiting electrode, adapted to be placed in a vicinity of a tertiary anodal longitudinal site of the nerve and to apply a tertiary anodal current to the nerve, the tertiary anodal longitudinal site being closer to the secondary anodal longitudinal site than to the primary anodal longitudinal site. In a preferred embodiment, the tertiary inhibiting anode is configured such that a current density of the tertiary anodal current is of lower magnitude than a magnitude of a current density of the secondary anodal current.

Preferably, the apparatus includes a housing, coupled to the cathode, the primary inhibiting anode and the secondary inhibiting anode, adapted to facilitate placement of the cathode and the anodes in the vicinities of their respective sites. In a preferred embodiment, the housing is configured such that an arc, defined by an extent that the housing is adapted to surround the nerve, is between about 90 and 270 degrees. Alternatively, the housing is configured such that an arc, defined by an extent that the housing is adapted to surround the nerve, is between about 270 and 359 degrees.

Typically, a closest cathode distance to an axis of the nerve, a closest primary inhibiting anode distance to the axis, and a closest secondary inhibiting anode distance to the axis are all at least approximately 1.5 times greater than the radius of the nerve.

For some applications, the secondary inhibiting anode is configured such that a secondary anodal current density induced by the secondary anodal current is of lower magnitude than a magnitude of a primary anodal current density induced by the primary anodal current. In a preferred embodiment, the primary anodal current is substantially of the same magnitude as the secondary anodal current. In a preferred embodiment, a characteristic surface area of the secondary inhibiting anode is higher than a characteristic surface area of the primary inhibiting anode. For example, the characteristic surface area of the secondary inhibiting anode may

be at least 2 times higher than the characteristic surface area of the primary inhibiting anode.

In a preferred embodiment, the secondary inhibiting anode is configured such that a current density of the secondary anodal current is of lower magnitude than a magnitude of a current density of the primary anodal current. In this case, a characteristic surface area of the primary inhibiting anode may be higher than a characteristic surface area of the secondary inhibiting anode, and a common voltage may be applied to the primary inhibiting anode and to the secondary inhibiting anode.

For some applications:

(a) the primary inhibiting anode is adapted to have associated therewith a primary level of electrical impedance between the primary inhibiting anode and the nerve, when in the vicinity of the primary anodal longitudinal site, and

(b) the secondary inhibiting anode is adapted to have associated therewith a secondary level of electrical impedance between the secondary inhibiting anode and the nerve when in the vicinity of the secondary anodal longitudinal site, the secondary level of impedance having a higher magnitude than the primary level of impedance.

In a preferred embodiment, the secondary inhibiting anode is adapted to be coupled to the housing so as to define a secondary anode distance to an axis of the nerve, and wherein the primary inhibiting anode is adapted to be coupled to the housing so as to define a primary anode distance to the axis of the nerve that is smaller than the secondary anode distance. For example, a ratio of the secondary anode distance to the primary anode distance may be greater than approximately 1.5 : 1.

In a preferred embodiment, the apparatus includes a primary fiber-selection anode, adapted to be placed in a vicinity of a primary fiber-selection anodal longitudinal site of the nerve that is closer to the cathodic longitudinal site than to the primary anodal longitudinal site. For example, the apparatus may include a secondary fiber-selection anode, adapted to be placed in a vicinity of a

secondary fiber-selection anodal longitudinal site of the nerve that is closer to the primary fiber-selection anodal longitudinal site than to the cathodic longitudinal site.

Preferably, the apparatus includes a control unit, adapted to drive the cathode to apply the cathodic current to the nerve, adapted to drive the primary inhibiting anode to apply the primary anodal current to the nerve, and adapted to drive the secondary inhibiting anode to apply the secondary anodal current to the nerve. In one preferred embodiment, the apparatus includes a first resistive element coupled between the control unit and the primary inhibiting anode, and a second resistive element coupled between the control unit and the secondary inhibiting anode, the second resistive element having a resistance higher than a resistance of the first resistive element.

For some applications, the apparatus includes exactly one lead that leaves the control unit for coupling the control unit to the primary and secondary inhibiting anodes. Alternatively, the apparatus includes respective leads that leave the control unit and couple the control unit to the primary and secondary inhibiting anodes.

The control unit is typically adapted to configure a current density of the secondary anodal current to be of lower magnitude than a current density of the primary anodal current. In a preferred embodiment, the control unit is adapted to configure an amplitude of a current density of the cathodic current to be between 1.1 and 2 times greater than an amplitude of a current density of the primary anodal current. Alternatively or additionally, the control unit is adapted to configure an amplitude of a current density of the cathodic current to be between 3 and 6 times greater than an amplitude of a current density of the secondary anodal current. Further alternatively or additionally, the control unit is adapted to configure an amplitude of a current density of the primary anodal current to be at least 2 times greater than an amplitude of a current density of the secondary anodal current.

There is also provided, in accordance with a preferred embodiment of the present invention, apparatus for applying current to a nerve having a radius and a longitudinal central axis, including:

a housing, adapted to be placed in a vicinity of the nerve; and

a cathode and an anode, fixed to the housing so as to define, when the housing is placed in the vicinity of the nerve, respective closest cathode and anode distances to the axis that are both at least approximately 1.5 times greater than the radius of the nerve.

Preferably, the closest cathode and anode distances to the axis are both at least approximately 2 times greater than the radius of the nerve.

In a preferred embodiment, the cathode includes a plurality of cathodes, placed in the vicinity of the cathodic longitudinal site of the nerve, at respective positions around the axis of the nerve, each of the respective positions being at a distance from the axis at least 1.5 times greater than the radius of the nerve.

In a preferred embodiment, the apparatus includes an insulating element disposed between the cathode and the anode. A characteristic distance of the insulating element to the axis of the nerve is typically at least 1.5 times greater than the radius of the nerve. For some applications, the distance of the anode to the axis is substantially the same as a characteristic distance of the insulating element to the axis of the nerve. For other applications, the distance of the anode to the axis is greater than a characteristic distance of the insulating element to the axis of the nerve. For example, the distance of the anode to the axis may be within 30% of the characteristic distance of the insulating element to the axis of the nerve plus a width of the anode.

There is further provided, in accordance with a preferred embodiment of the present invention, apparatus for applying current to a nerve having a radius and a longitudinal central axis, including:

a housing, adapted to be placed in a vicinity of the nerve;

first and second electrodes, fixed to the housing; and

an insulating element, fixed to the housing between the first and second electrodes so as to define a characteristic closest insulating element distance to the central axis that is at least approximately 1.5 times greater than the radius of the nerve.

In a preferred embodiment, the insulating element is adapted to be placed in the vicinity of the nerve at a longitudinal site that is between respective longitudinal sites of the first and second electrodes. Alternatively, the insulating element is adapted to be placed in the vicinity of the nerve at a site with respect to the axis of the nerve that is between respective sites of the first and second electrodes, with respect to the axis.

There is still further provided, in accordance with a preferred embodiment of the present invention, apparatus for applying current to a nerve, including:

a cathode, adapted to be placed in a vicinity of a cathodic site of the nerve; and

a plurality of anodes, adapted to be placed in a vicinity of respective anodal longitudinal sites of the nerve and to apply respective anodal currents to the nerve, that define, in combination, an anodal activation function having: (a) a hyperpolarizing portion thereof having a maximum hyperpolarizing amplitude, and (b) a depolarizing portion thereof, having a maximum depolarizing amplitude corresponding to a depolarizing site on the nerve distal with respect to the cathode to a site corresponding to the hyperpolarizing portion, wherein the maximum hyperpolarizing amplitude is at least five times greater than the maximum depolarizing amplitude.

In a preferred embodiment, the apparatus includes a housing to which the cathode and the plurality of anodes are coupled, wherein a distance of a first one of the anodes to an axis of the nerve is less than a distance of a second one of the anodes to the axis, the first one of the anodes being coupled to the housing closer to the cathode than the second one of the anodes.

Alternatively or additionally, the apparatus includes a housing to which the cathode and the plurality of anodes are coupled, wherein a surface area of a first

one of the anodes is less than a surface area of a second one of the anodes, the first one of the anodes being coupled to the housing closer to the cathode than the second one of the anodes.

Preferably, the apparatus includes a housing to which the cathode and the plurality of anodes are coupled, and one of the anodes is positioned within the housing so as to reduce a virtual cathode effect induced by another one of the anodes.

The cathode and anodes are typically disposed such that a first one of the anodal longitudinal sites is between the cathodic site and a second one of the anodal longitudinal sites. In a preferred embodiment, the anodes are disposed such that the second one of the anodal longitudinal sites is between the first one of the anodal longitudinal sites and a third one of the anodal longitudinal sites. Preferably, the anodes are adapted such that a current density of the anodal current applied at the second one of the anodal longitudinal sites has a lower magnitude than a magnitude of a current density of the anodal current applied at the first one of the anodal longitudinal sites.

For some applications, the anodes are adapted such that a ratio of the current density of the anodal current applied at the first site to the current density of the anodal current applied at the second site is at least 2:1. Preferably, the anodes are adapted such that a ratio of the current density of the anodal current applied at the first site to the current density of the anodal current applied at the second site is at least 5:1.

There is yet further provided, in accordance with a preferred embodiment of the present invention, apparatus for applying current to a nerve, including:

a cathode, adapted to be placed in a vicinity of a first longitudinal site of the nerve; and

an elongated anode, adapted to be placed in a vicinity of a second longitudinal site of the nerve, and, when so placed, to have associated therewith: (a) a first level of electrical impedance between the nerve and a location on the elongated anode proximal to the cathode, and (b) a second level of electrical

impedance, greater than the first level, between the nerve and a location on the elongated anode distal to the cathode.

Preferably, the apparatus includes a coating disposed on a surface of the elongated anode, configured to provide the first and second levels of impedance. In a preferred embodiment, the coating is disposed on the surface in different respective thicknesses at the two locations on the elongated anode. Alternatively or additionally, the coating includes a coating that has undergone a surface treatment, and wherein the coating is configured to provide the first and second levels of impedance responsive to having undergone the surface treatment. In a preferred embodiment, the coating includes iridium oxide, titanium nitrite, and/or platinum iridium.

There is also provided, in accordance with a preferred embodiment of the present invention, apparatus for applying current to a nerve having a longitudinal axis, including:

two or more electrodes, adapted to be placed in a vicinity of a longitudinal site of the nerve, at respective positions around the axis; and

a control unit, adapted to:

(a) drive current between two of the electrodes, thereby defining a first pair of the electrodes and a first direction of current flow, and, less than one millisecond later,

(b) drive current between two of the electrodes, thereby defining a second pair of the electrodes and a second direction of current flow, and

(c) cycle between steps (a) and (b) at a rate greater than 1000 Hz,

wherein at least either the first pair of electrodes is different from the second pair of electrodes or the first direction of current flow is different from the second direction of current flow.

Typically, the two or more electrodes include three or more electrodes, or four or more electrodes.

For some applications, the control unit is adapted to set the rate to be greater than 4000 Hz.

There is yet additionally provided, in accordance with a preferred embodiment of the present invention, apparatus for applying current to a nerve having a longitudinal axis, including:

a set of two or more cathodes, adapted to be placed in a vicinity of a cathodic longitudinal site of the nerve, at respective positions around the axis; and

a set of two or more anodes, adapted to be placed in a vicinity of an anodal longitudinal site of the nerve, at respective positions around the axis.

As appropriate, the two or more cathodes may include six or more cathodes, e.g., twelve or more cathodes.

The apparatus typically includes a control unit, adapted to drive current between respective ones of the cathodes and respective ones of the anodes. The control unit is preferably adapted to cycle the current driving at a rate greater than 1000 Hz. In a preferred embodiment, the control unit is adapted to complete a sweep of driving the current through substantially all of the cathodes in less than 1000 microseconds. Preferably, the control unit is adapted to complete a sweep of driving the current through substantially all of the cathodes in less than 100 microseconds.

There is still additionally provided, in accordance with a preferred embodiment of the present invention, a method for applying current to a nerve, including:

applying cathodic current in a vicinity of a cathodic longitudinal site of the nerve;

applying a primary anodal current to the nerve in a vicinity of a primary anodal longitudinal site of the nerve; and

applying a secondary anodal current to the nerve in a vicinity of a secondary anodal longitudinal site of the nerve that is closer to the primary anodal longitudinal site than to the cathodic longitudinal site.

There is yet additionally provided, in accordance with a preferred embodiment of the present invention, a method for applying current to a nerve

having a radius and a longitudinal central axis, including applying cathodic and anodal current to the nerve from respective cathodic and anodal current-application sites that are both located at distances from the axis of the nerve which are at least approximately 1.5 times greater than the radius of the nerve.

There is also provided, in accordance with a preferred embodiment of the present invention, a method for applying current to a nerve, including:

applying cathodic current in a vicinity of a cathodic site of the nerve; and

applying anodal currents in a vicinity of respective anodal longitudinal sites of the nerve, the currents defining, in combination, an anodal activation function having: (a) a hyperpolarizing portion thereof having a maximum hyperpolarizing amplitude, and (b) a depolarizing portion thereof, having a maximum depolarizing amplitude corresponding to a depolarizing site on the nerve distal, with respect to the cathodic site, to a site corresponding to the hyperpolarizing portion, wherein the maximum hyperpolarizing amplitude is at least five times greater than the maximum depolarizing amplitude.

There is further provided, in accordance with a preferred embodiment of the present invention, a method for applying current to a nerve having a longitudinal axis, including driving current between: (a) a set of two or more cathodic sites in a vicinity of a first longitudinal site of the nerve, which are located at respective positions around the axis, and (b) a set of two or more anodal sites in a vicinity of a second longitudinal site of the nerve, which are located at respective positions around the axis.

There is still further provided, in accordance with an embodiment of the present invention, apparatus including an implantable tubular cuff, the cuff:

shaped so as to define: (a) a longitudinal slit having a first edge and a second edge, and (b) at least one hole in a vicinity of the first edge; and

including at least one protrusion, which is coupled to the cuff in a vicinity of the second edge, and is adapted to hold the first and second edges together when

the protrusion is passed through the hole and when the cuff is disposed within a body of a subject and surrounding longitudinal tissue of the subject.

For some applications, the cuff is shaped so as to define a plurality of holes in the vicinity of the first edge, and the cuff includes a plurality of protrusions, which are coupled to the cuff in the vicinity of the second edge, and are adapted to hold the first and second edges together when each of the protrusions is passed through a respective one of the holes.

In an embodiment, the cuff includes at least one electrode. For some applications, the cuff includes two electrodes and an insulating element disposed therebetween.

In an embodiment, the cuff includes a first flexible resilient material, and the insulating element includes a second flexible resilient material, the first material having a hardness different from a hardness of the second material.

In an embodiment, the cuff includes a tab coupled to the first edge, the tab configured to aid in drawing the protrusion through the hole when the tab is moved toward the protrusion.

For some applications, the cuff includes at least one flexible resilient material having a Shore D hardness between about 4 and about 80.

In an embodiment, the cuff includes a first flexible resilient material in a vicinity of the hole, and a second flexible resilient material, the first material having a hardness different from a hardness of the second material. In an embodiment, the cuff includes a first flexible resilient material in a vicinity of the protrusion, and a second flexible resilient material, the first material having a hardness different from a hardness of the second material.

In an embodiment, the cuff includes a filament coupled to the protrusion. For some applications, the filament is formed as an integral portion of the cuff. For some applications, the cuff is configured so that when the filament is drawn through the hole, the protrusion is drawn through the hole thereafter.

In an embodiment, the tissue includes a nerve of the subject, and the cuff is adapted to be placed around the nerve. Alternatively, the tissue includes a blood vessel of the subject, and the cuff is adapted to be placed around the blood vessel. Further alternatively, the tissue is selected from the list consisting of: a muscle of the subject, a tendon of the subject, a ligament of the subject, an esophagus of the subject, intestine of the subject, and a fallopian tube of the subject, and the cuff is adapted to be placed around the selected tissue.

In an embodiment, the first edge includes a flap, adapted to come in contact with a portion of the cuff in the vicinity of the second edge when the first and second edges are held together. For some applications, when no external force is applied to the cuff, the flap forms an angle of between about 90 and about 180 degrees with a surface of the cuff in the vicinity of the first edge. For some applications, the flap includes a tab, configured to help draw the protrusion through the hole when the tab is moved toward the protrusion.

In an embodiment, each of the protrusions includes a head portion and a neck portion, the head portion having a perimeter greater than a perimeter of the neck portion. For some applications, a perimeter of the head portion is greater than a perimeter of the hole.

For some applications, the protrusion is adapted to be passed through the hole such that the head portion passes through the hole, and the neck portion remains substantially in the hole. For some applications, the head portion has an initial shape prior to being passed through the hole, and is adapted to (a) assume a different shape while being passed through the hole, and (b) substantially return to the initial shape thereof after being passed through the hole.

For some applications, the head portion includes a first flexible resilient material having a first hardness, and a portion of the cuff excluding the head portion includes a second flexible resilient material having a second hardness, the first hardness different from the second hardness. For some applications, the cuff includes a filament coupled to the neck portion.

In an embodiment, the cuff is configured so that when the filament is drawn through the hole, the head portion is drawn through the hole thereafter.

There is additionally provided, in accordance with an embodiment of the present invention, a method for enclosing a section of longitudinal tissue of a subject with a tubular cuff, the method including:

separating a first edge of a longitudinal slit defined by the cuff from a second edge of the slit;

placing the cuff within a body of the subject around the section of the tissue; and

passing at least one protrusion coupled to the cuff in a vicinity of the first edge, through at least one hole defined by the cuff in a vicinity of the second edge, so as to hold the first and second edges together.

There is yet additionally provided, in accordance with an embodiment of the present invention, a method for stimulating a vagus nerve of a subject, including:

applying to the vagus nerve a first electrode device, the first electrode device having a first characteristic diameter;

driving the electrodes of the first electrode device to apply a current to the vagus nerve;

measuring a reduction in heart rate of the subject responsive to driving the electrodes of the first electrode device to apply the current;

determining whether the reduction in heart rate is less than about 10%; and

responsive to determining that the reduction in heart rate is less than about 10%, removing the first electrode device from the nerve and applying to the vagus nerve a second electrode device, the second electrode device having a second characteristic diameter smaller than the first characteristic diameter.

For some applications, applying the first electrode device includes:

applying the first electrode device, wherein the first characteristic diameter corresponds to a characteristic distance of electrodes of the first electrode device

from an axis of the nerve when the first electrode device is applied to the nerve, and wherein the second characteristic diameter corresponds to a characteristic distance of electrodes of the second electrode device from an axis of the nerve when the second electrode device is applied to the nerve, the second characteristic distance being smaller than the first characteristic distance.

Alternatively or additionally, applying the first electrode device includes:

applying the first electrode device, wherein the first characteristic diameter corresponds to a characteristic distance of an insulating element of the first electrode device from an axis of the nerve when the first electrode device is applied to the nerve, and wherein the second characteristic diameter corresponds to a characteristic distance of an insulating element of the second electrode device from an axis of the nerve when the second electrode device is applied to the nerve, the second characteristic distance being smaller than the first characteristic distance.

The present invention will be more fully understood from the following detailed description of the preferred embodiments thereof, taken together with the drawings, in which:

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1A is a schematic, cross-sectional illustration of an electrode assembly for applying current to a nerve, in accordance with a preferred embodiment of the present invention;

Fig. 1B is a schematic pictorial illustration of the electrode assembly of Fig. 1A, in accordance with a preferred embodiment of the present invention;

Figs. 2A and 2B are schematic, cross-sectional illustrations of other electrode assemblies for applying current to a nerve, in accordance with respective preferred embodiments of the present invention;

Figs. 3A, 3B, and 3C are schematic, cross-sectional illustrations of yet other electrode assemblies for applying current to a nerve, in accordance with respective preferred embodiments of the present invention;

Fig. 4 is a schematic, cross-sectional illustration of still another electrode assembly for applying current to a nerve, in accordance with a preferred embodiment of the present invention;

Fig. 5 is a schematic, pictorial illustration of an additional electrode assembly for applying current to a nerve, in accordance with a preferred embodiment of the present invention;

Fig. 6 is a graph modeling a calculated activation function over a range of distances from the central axis of a nerve to which current is applied using an electrode assembly such as that shown in Fig. 1A, in accordance with a preferred embodiment of the present invention;

Fig. 7 is a graph modeling a calculated activation function over a portion of the length of a nerve to which current is applied using an electrode assembly such as that shown in Fig. 2A, in accordance with a preferred embodiment of the present invention;

Figs. 8 and 9 are schematic pictorial illustrations of a tubular cuff in a slightly opened position and a closed position, respectively, in accordance with an embodiment of the present invention;

Fig. 10 is a cross-sectional view of the cuff of Figs. 8 and 9 in a closed position in the plane A--A of Fig. 9, in accordance with an embodiment of the present invention;

Fig. 11 is a cross-sectional view of a protrusion of the cuff of Figs. 8 and 9, in accordance with an embodiment of the present invention;

Fig. 12 is a cross-sectional view of another tubular cuff in a slightly opened position, in accordance with an embodiment of the present invention;

Figs. 13 and 14 are cross-sectional views of the cuff of Fig. 12 in a slightly opened position and a closed position, respectively, in accordance with an embodiment of the present invention;

Fig. 15 is an enlarged schematic pictorial illustration of a protrusion of the cuff of Figs. 8 and 9, in accordance with an embodiment of the present invention;

Fig. 16 is a schematic, cross-sectional illustration of the cuff of Figs. 8 and 9 in the plane B--B of Fig. 9, in accordance with an embodiment of the present invention; and

Fig. 17 is an enlarged cross-sectional view of a portion of the cuff of Figs. 8 and 9 in a closed position, in accordance with an embodiment of the present invention.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Reference is now made to Figs. 1A and 1B. Fig. 1A is a schematic, cross-sectional illustration of an electrode assembly 20 for applying current to a nerve 30, in accordance with a preferred embodiment of the present invention. Fig. 1B is a schematic pictorial illustration of electrode assembly 20, in accordance with a preferred embodiment of the present invention. It is noted that although the various electrode assemblies shown in the figures generally contain cylindrical configurations of their elements, other geometrical configurations, such as non-rotationally symmetric configurations, are also suitable for applying the principles of the present invention. In particular, a housing 22 of the electrode assembly (and the electrodes themselves) may form a complete circle around the nerve, or it may define an arc between approximately 0 and 90 degrees, between 90 and 180 degrees, between 180 and 350 degrees, or between 350 and 359 degrees around the nerve. (One such preferred embodiment, shown in Fig. 1B, includes the housing and the electrodes defining an arc of 270 degrees.)

Preferably, the electrode assembly comprises a cathode 40, a primary inhibiting anode 42, and a secondary inhibiting anode 44. Each of these electrodes is fixed within housing 22 of the electrode assembly. Insulating elements 24, which are typically either part of the body of the housing or affixed thereto, are preferably placed so as to separate the electrodes, and to guide current from one of the electrodes towards the nerve prior to being taken up by another one of the electrodes. Preferably (as shown), the insulating elements are closer to nerve 30

than are the electrodes. Alternatively (not shown), insulating elements 24 are generally flush with the faces of the electrodes.

Typically, cathodic current driven through cathode 40 by a control unit (not shown) stimulates fibers within nerve 30 to generate action potentials which travel in both directions within the nerve -- i.e., towards anodes 42 and 44 ("the anodal direction"), and in the opposite direction, out of housing 22, towards a target ("the target direction"). Anodal current driven through anode 42, by contrast, is typically applied so as to inhibit the action potentials which were induced by the cathodic current, and which subsequently traveled in the anodal direction.

For most applications, current applied by secondary inhibiting anode 44 is of lower magnitude than the current applied by primary inhibiting anode 42. In this manner, the "virtual cathode" effect induced by the primary anodal current is minimized. In accordance with a preferred embodiment of the present invention, application of the primary and secondary anodal currents in appropriate ratios is configured to generally minimize the virtual cathode effect. Typically, but not necessarily, the ratio of the primary to the secondary anodal current ranges from 2:1 to 10:1.

Fig. 2A is a schematic, cross-sectional illustration of an electrode assembly 60, in accordance with another preferred embodiment of the present invention. Electrode assembly 60 comprises a cathode 70, a primary inhibiting anode 72, and a secondary inhibiting anode 74, which are typically driven in a manner analogous to that described hereinabove with respect to cathode 40 and primary and secondary inhibiting anodes 42 and 44.

Preferably, electrode assembly 60 additionally comprises a tertiary anode 76, which is employed to reduce any virtual cathode effect which may be induced by secondary inhibiting anode 74. For example, relative to a normalized cathodic current of -1, the primary inhibiting anode, secondary inhibiting anode, and tertiary anode may be configured to apply respective currents of 0.66, 0.25, and 0.09. Typically, the magnitude of the current from the tertiary anode is sufficiently small, such that the virtual cathode effect resulting therefrom does not

generate action potentials that interfere with the performance of electrode assembly 60. For some applications, however, particularly when the current from primary inhibiting anode 72 is relatively high, additional anodes (not shown) are provided in electrode assembly 60.

Electrode assembly 60 preferably comprises a primary fiber-selection anode 78, adjacent to cathode 70 and on the other side of the housing from anodes 72, 74, and 76. The current applied by cathode 70 typically induces bi-directional action potential propagation in fibers in nerve 30 having a range of diameters. In order to block propagation past anode 78 of those action potentials traveling in relatively larger fibers, the primary fiber-selection anode is preferably driven to apply anodal current configured to block action potential propagation in these larger fibers of nerve 30, and configured not to block action potential propagation in the smaller fibers. In particular, since the larger fibers are generally more sensitive to being blocked by a lower level of anodal current than are the smaller fibers, a given level of current applied through fiber-selection anode 78 typically blocks action potentials in the larger fibers, while allowing passage of action potentials induced by the current from cathode 70 and traveling in the small fibers. Therefore, action potentials induced by the cathode continue to propagate in the smaller fibers, past primary fiber-selection anode 78, out of housing 22, and towards a target site. By increasing the current driven through the primary fiber-selection anode, progressively smaller fibers are inhibited from propagating action potentials. Conversely, by decreasing the application of current through primary fiber-selection anode 78, larger fibers are able to propagate action potentials.

For applications in which the current applied through primary fiber-selection anode 78 is sufficient to create a substantial virtual cathode effect, a secondary fiber-selection anode 80 is preferably incorporated into electrode assembly 60, adjacent to the primary fiber-selection anode and on the far side of cathode 70. In a fashion analogous to that described hereinabove with respect to secondary inhibiting anode 74, secondary fiber-selection anode 80 is preferably driven to apply a current to the nerve smaller than that applied by primary fiber-selection anode 78, so as to counteract the virtual cathode effect which would

otherwise, in some circumstances, induce action potential propagation responsive to the current applied by primary fiber-selection anode 78.

Preferably, fixed ratios for the currents applied by anodes 72, 74, 76, 78, and 80 are pre-defined and are set in hardware, e.g., by a set 82 of resistors R1, R2, R3, R4, and R5, which couple a single lead 86 coming from a control unit 90 to the respective anodes. Typically, a guide tube 88 conveys lead 86, in combination with a second lead 84 that drives cathode 70, from control unit 90 to electrode assembly 60. Advantageously, this embodiment provides control over multiple anodes, and corresponding reduction of the virtual cathode effect, with a minimum number of leads.

Alternatively, for some applications (not shown), particularly when cathodic and anodal current parameters vary over a wide range, the various anodes are independently driven by the control unit via respective leads, so as to optimize the minimization of the virtual cathode effect and the maximization (when appropriate) of anodally-induced hyperpolarization. For some applications, a combination of the two techniques described are utilized, whereby, for example, anodes 72, 74, and 76 are driven by current in a single lead, and anodes 78 and 80 are driven by current in two additional, separate leads.

Preferably, electrode assembly 60 (as well as the other electrode assemblies described herein, as appropriate) has physical dimensions configured so as to provide a relatively uniform activation function across the cross-section of nerve 30. The distance L1 separating the central longitudinal axis of nerve 30 from cathode 70 and from anodes 72, 74, 76, 78, and 80 is typically at least approximately 1.5 times greater than the radius L0 of the nerve. For many applications, L1 is greater than two times L0. By placing the cathode and anodes at such distances, increased electrical field uniformity is obtained within the nerve, particularly as the gradients in the activation function are largest near the electrodes, and are significantly reduced across the cross-section of the nerve. This, in turn, increases the ability of control unit 90 to assure that most fibers within the nerve will experience generally the same level of applied currents.

Insulating elements 24 preferably separate cathode 70 from anodes 72 and 78. For some applications, additional insulating elements 24 separate the various adjacent anodes in electrode assembly 60. The insulating elements define a characteristic closest "insulating element distance" L2 to the axis of nerve 30 that is preferably at least approximately 1.5 times greater than L0. It will be appreciated that for structural reasons, spokes or other offshoots of the insulating elements may come closer to the nerve. However, the "functional" portions of the insulating elements, i.e., those portions which provide a substantial effect on the direction of current flow between the electrodes and through the nerve, preferably remain at a closest distance L2 of at least 1.5 * L0. For some applications, particularly those in which battery life is a pressing factor, L2 is set to be less than 1.5 * L0, at the expense of some uniformity of the applied field.

Typically, L1 is greater than or equal to L2. For anode and cathode widths w, preferred values for L1 are in the range $L2 < L1 < 1.5 (L2 + w)$. Further preferably, $L2 + 0.5w < L1 < L2 + w$. Typically, the width w of the electrodes is approximately equal to 0.5 * L0. (The width w, as well as other dimensions, are not drawn to scale in the figures.) In accordance with a preferred embodiment of the present invention, when L0 is between 1 and 2 mm, L2 is preferably between 1.5 and 3 mm, L1 is between 1.5 and 4 mm, and w is between 0.5 and 1 mm.

Fig. 2B is a schematic, cross-sectional illustration of an electrode assembly 61, in accordance with another preferred embodiment of the present invention. Electrode assembly 61 is generally similar to electrode assembly 60, described hereinabove with reference to Fig. 2A, except for differences as described.

Whereas in electrode assembly 60, insulating elements 24 all had generally equal dimensions, electrode assembly 61 provides each of five insulating elements 24A, 24B, 24C, 24D, and 24E with a respective (typically different) distance to the axis of nerve 30 of L2(A), L2(B), L2(C), L2(D), and L2(E). In general, as the distance L2(x) for any given one of the insulating elements decreases, the current density experienced by the nerve in a vicinity of the insulating element increases. Thus, for example, in the preferred embodiment shown in Fig. 2B, L2(C)

corresponding to insulating element 24C is relatively large, such that the current density in the nerve near anode 76 is low.

Fig. 3A is a schematic, cross-sectional illustration of an electrode assembly 110, in accordance with a preferred embodiment of the present invention. Electrode assembly 110 is analogous to electrode assembly 20, described hereinabove with reference to Fig. 1A, except for differences as described. A cathode 120 of electrode assembly 110 serves generally the same purpose as cathode 40, while an elongated anode 122 preferably replaces anodes 42 and 44. Typically, elongated anode 122 is 0.5 mm - 10 mm in length, although it may be longer or shorter responsive to the level of currents expected to be applied therethrough.

Elongated anode 122, when placed on or over nerve 30, preferably has at least two levels of electrical impedance associated therewith, between respective sites on the elongated anode and the nerve. A biological material 92, typically including fibrous tissue and body fluids, generally occupies some of the space between the electrodes and the nerve. The impedance governing the passage of current from elongated anode 122 to nerve 30 is therefore typically a function of the properties of biological material 92. Additionally, a resistive element 124 (e.g., a shaped iridium oxide coating, a titanium nitrite coating, or a platinum iridium coating) preferably provides greater electrical impedance distal to cathode 120 than proximal thereto. In a preferred embodiment, the coating undergoes a surface treatment (e.g., "sand blasting" or a chemical treatment), in which the effective microscopic surface area is increased by the treatment. Preferably, the proximal-to-the-cathode end of the coating is more heavily treated by the surface treatment, and therefore has lower impedance. Alternatively or additionally, the geometry of the elongated anode is configured so as to effect the change in impedance as described.

Typically, the anodal current leaving the portion of elongated anode 122 distal to cathode 120 minimizes the virtual cathode effect induced thereat by anodal current leaving the portion of elongated anode 122 proximal to cathode 120.

Fig. 3B is a schematic, cross-sectional illustration of an electrode assembly 111, in accordance with a preferred embodiment of the present invention. Preferably, a current density in a vicinity of a primary anode 123 is higher than a current density in a vicinity of a secondary anode 124. The difference in current densities is preferably attained by having a width w2 of anode 124 be at least 2 - 10 times higher than a corresponding width w1 of anode 123. In this manner, when generally the same current is passed through both anodes, the current density --and thus the hyperpolarizing effect on the activation function-- is greater near anode 123 than near anode 124.

Fig. 3C is a schematic, cross-sectional illustration of an electrode assembly 112, in accordance with a preferred embodiment of the present invention. In this embodiment, the distance L1(B) between a primary anode 125 and the axis of nerve 30 is preferably smaller than the distance L1(A) between a secondary anode 126 and the axis of the nerve. The distance of cathode 120 from the axis is similar to L1(A) (as shown), while in other embodiments (not shown) the distance is closer to L1(B). In a manner similar to that described with reference to Fig. 3B, the geometrical configuration of the cathode and the anodes shown in Fig. 3C typically provides higher current density near the anode that is proximal to the cathode, and provides generally lower current density near the anode that is distal to the cathode.

Fig. 4 is a schematic, cross-sectional illustration of an electrode assembly 140 surrounding nerve 30, which is driven by a control unit 160 to apply current to the nerve, in accordance with a preferred embodiment of the present invention. Two or more electrodes 150 fixed to a housing 142 are placed at respective positions around the axis. Typically, electrodes 150 comprise at least three, and preferably four or more electrodes. In this case, insulating elements 144 are preferably disposed between adjacent electrodes. If there are only two electrodes, then control unit 160 preferably alternates the direction of the current driven between the two electrodes at a rate greater than 1000 Hz.

When there are three or more electrodes 150, thereby defining a ring of electrodes, control unit 160 preferably cycles its driving of the electrodes in

accordance with a stimulation protocol. For example, one such protocol for three electrodes may include driving current between electrodes 1 and 2, then 2 and 3, then 3 and 1, then 1 and 2, etc., cycling through the combinations at an average rate of greater than 1000 Hz, or, for some applications, greater than 10,000 Hz. For larger numbers of electrodes, e.g., 6, 12, or 24, the stimulation cycling protocol is typically more complex, and is preferably configured to cause current to pass through or close to most or all fibers in the nerve at the longitudinal site where the ring of electrodes is placed. One such complex protocol includes effectively creating a star out of successive current lines passing through the nerve. In Fig. 4, an initial set of four such lines 152, 154, 156, and 158 are shown.

Fig. 5 is a schematic, pictorial illustration of an electrode assembly 170, in accordance with another preferred embodiment of the present invention. Electrode assembly 170 comprises an anodal ring 172 of two or more anodes and a cathodic ring 192 of two or more cathodes. In the preferred embodiment shown in Fig. 5, anodal ring 172 comprises anodes 174, 176, 178, 180, 182, and 184, and cathodic ring 192 comprises cathodes 194, 196, 198, 200, 202, and 204. Each ring of electrodes is placed around the nerve axis, at a respective anodal or cathodic longitudinal site of the nerve.

Preferably, a control unit drives anode 176 to drive current through nerve 30 to cathode 196, in order to initiate generation of action potentials near cathode 196 and/or near a substantial portion of cathodic ring 192. Cathode 196 and anode 176 are preferably at mutually-opposed orientations with respect to the axis. In this manner, a greater portion of the current from anode 176 enters nerve 30 than if, for example, the control unit were to drive anode 176 to send the same amount of charge to cathode 202. In this latter case, a substantial portion of the current leaving anode 176 would travel directly through the biological material surrounding nerve 30, and not enter into nerve 30.

In the example shown in Fig. 5, after anode 176 sends current to cathode 196, anode 178 sends current to cathode 198, and then anode 180 sends current to cathode 200. Preferably, an entire sweep of all of the electrodes in the two rings is accomplished within 0.01 - 1 millisecond.

Advantageously, by utilizing discrete electrodes arranged into a ring of cathodes and a ring of anodes, each located at respective longitudinal sites on the nerve, fibers in the nerve are stimulated near the ring of cathodes, and inhibited near the ring of anodes, typically using substantially less current than if a solid anode ring and a solid cathode ring were placed around the nerve. Further advantageously, steering of current to traverse or avoid certain regions in the cross-section of the nerve is readily attainable, using the techniques described herein, by suitable activation of the cathodes and/or anodes.

For simplicity, Fig. 5 shows only a single anodal ring 172. It is noted that the use of rings of anodes and/or a ring of cathodes is preferably also applied, as appropriate, in combination with the cathode - anode - anode configuration of Figs. 1A and 1B, or in combination with the anode - anode - cathode - anode - anode - anode configuration of Figs. 2A and 2B. In a preferred embodiment, some of the electrodes (e.g., cathode 70 and anodes 72 and 78) comprise multiple electrodes disposed in a ring, while others of the electrodes (e.g., anodes 74, 76, and 80) are generally solid rings, each comprising only a single ring.

Fig. 6 is a graph modeling calculated activation function over a range of distances from the central axis of a nerve, in accordance with a preferred embodiment of the present invention. The graph models, in a simplified fashion, the activation function, at a cathodic site, produced in response to application of current by, for example, electrode assembly 20 (Fig. 1A) or electrode assembly 60 (Fig. 2A). The equation producing the graph shown in Fig. 6 is:

$$AF(r) = \frac{I}{2\partial} \int_0^{2\partial} \left[1 + \left(\frac{r}{R}\right)^2 - 2\left(\frac{r}{R}\right) \cos \ddot{o} \right]^{-1.5} d\ddot{o},$$

where r is the radius from the central axis of the nerve, and R is the distance of an electrode ring from the axis. L0 in the figure shows the radius of a typical nerve, and L2 shows the distance to an insulating element. As noted above, the amount of change of the activation function within the nerve ($r < L0$) is significantly smaller than the amount of change of the activation function outside the nerve ($r > L0$).

Fig. 7 is a graph modeling calculated activation function over a portion of the length of nerve 30, when current is applied using an electrode assembly such as that shown in Fig. 2A (without applying current through anodes 78 and 80), in accordance with a preferred embodiment of the present invention. For the purposes of modeling the activation function, cathode 70 is placed at a longitudinal site on the nerve labeled z = -3 (in relative units), and anodes 72, 74, and 76 are placed at longitudinal positions z = 0, 1.4, and 2.7. Anodes 72, 74, and 76 are driven to apply currents A1 = 0.66, A2 = 0.25, and A3 = 0.09, respectively. Each one of the electrodes generates its own activation function responsive to the applied currents, as modeled in Fig. 7.

The top three data lines in Fig. 7 show that each of the anodes generates a depolarization portion (most clearly seen for applied current A1) and a hyperpolarization portion (clearly seen for each anode). It is noted that the depolarization portion of the activation function generated by the largest applied anodal current (A1) at approximately z = 1.2 is substantial, and, in many cases, is sufficient to stimulate fibers within the nerve.

The sum of the effect of each of the anodal activation functions is seen in the fourth data line in Fig. 7, labeled "summed anodes." This line demonstrates that the hyperpolarization portion of the activation function due to anodal current A2 significantly counteracts the depolarization portion of the activation function due to anodal current A1. Advantageously, the peaks 222 at $z > 0$ are generally not of sufficient magnitude to excessively stimulate the nerve fibers within nerve 30 by means of the virtual cathode effect. Nevertheless, the maximum hyperpolarization peak 220 of the "summed anodes" curve remains strong, sufficient to inhibit action potential propagation in a substantial proportion of the fibers of nerve 30. The ratio of the magnitude of peak 220 to the magnitude of the highest of depolarization peaks 222 is typically at least 8:1, and is preferably greater than 10:1.

The bottom data line in Fig. 7 shows the combined effect on the activation function due to the summed anode activation function and the activation function due to the cathode. It is noted that the use of the various anodes does not

excessively decrease either the magnitude of the desired depolarizing peak 230, or that of the desired hyperpolarizing peak 240 of the combined activation function.

Reference is now made to Figs. 8 and 9, which are schematic pictorial illustrations of a tubular cuff 300 in a slightly opened position and a closed position, respectively, in accordance with an embodiment of the present invention. For some applications, such as those described hereinabove or in the patent applications referenced hereinbelow, cuff 300 is adapted to surround and enclose a nerve of a subject. Alternatively, cuff 300 is adapted to surround and enclose other generally tubular tissue of the subject, such as a blood vessel, a muscle, a tendon, a ligament, an esophagus, intestine, or a fallopian tube. For example, cuff 300 may be placed around a blood vessel in order to prevent rupture of an aneurysm.

Cuff 300 defines a central lumen 304 and a longitudinal slit 306, as best seen in Fig. 8. A first edge 308 of the cuff is brought in contact with a second edge 310 thereof in order to close the cuff around tubular tissue passing through lumen 304. Cuff 300 defines one or more holes 312 passing therethrough, in a vicinity of first edge 308, as seen in Fig. 8. In a vicinity of second edge 310, the cuff comprises one or more protrusions 314, generally corresponding to the number of holes 312. When protrusions 314 are passed through respective holes 312, the protrusions engage the holes, thereby closing the cuff around the tubular tissue. Cuff 300 typically may be repeatedly opened and closed by a surgeon. The number of protrusions and holes which cuff 300 comprises depends on the length of the cuff and the specific application. For example, when cuff 300 has a length of about 1 cm and is adapted for coupling to a nerve, the cuff typically comprises one, two, or three protrusions.

Fig. 10 is a cross-sectional view of cuff 300 in a closed position in the plane A--A of Fig. 9, in accordance with an embodiment of the present invention. In this embodiment, protrusion 314 comprises a head portion 316 and a neck portion 318, which is narrower than the head portion. To couple first edge 308 to second edge 310, head portion 316 is drawn through hole 312. Since head portion 316 and cuff 300 comprise a flexible material, as described hereinbelow, the head

portion is able to be drawn through hole 312, even thought the hole is smaller than the head portion. Once the head portion emerges from the hole, the head portion and hole typically return to substantially their initial respective shapes. The head portion thus typically remains in place unless the first and second edges are deliberately drawn apart by a force greater than that which naturally occurs in the environment in which cuff 300 is typically used (e.g., surrounding a nerve or blood vessel). As can be seen in Fig. 10, when cuff 300 is in a closed position, neck portion 318 of protrusion 314 typically occupies substantially all of hole 312, and, in the plane A--A, a portion 320 of first edge 308 is separated from the remainder of first edge 310 by hole 312.

Although head portion 316, neck portion 318, and hole 312 are shown in the figures as generally rectangular in shape, this is by way of example only. In actual implementations, these elements may have various shapes, such as squares, circles, or ellipses. Additionally, these three elements need not all have the same shape; for example, the hole and neck portion may be rectangular, while the head portion is circular. Alternatively, the hole may be simply a slit in the material of the cuff, and the protrusion passes through the slit.

For use of cuff 300 with a nerve, a thickness T of the wall of cuff 300, at the wall's thinnest point, is typically between about 0.1 and 10 mm. An internal diameter D of the cuff at its widest point is typically between about 0.1 and 50 mm. Typically, a length L of hole 312 (Fig. 8) is between about 0.5 and about 5 mm, and a width W of the hole is between about 0 and about 5 mm. (It is noted that a width of 0 mm corresponds to the hole being a slit.)

Reference is again made to Fig. 9. For some applications, first edge 308 comprises a flap 322. A region of contact 324 between the inner surface of the flap and the outer surface of second edge 310 typically serves as a good mechanical and electrical seal when cuff 300 is in its closed position. This good seal generally prevents the ingrowth of tissue, which sometimes occurs when conventional cuffs are implanted on a long-term basis.

Fig. 11 is a cross-sectional view of protrusion 314, in accordance with an embodiment of the present invention. Cuff 300 comprises one or more filaments 326, such as sutures or filaments made from silicone, each of which is coupled to one of protrusions 314, typically to neck portion 318 thereof. For example, the filament may be passed around the neck portion and knotted at the time of manufacture of cuff 300, so that both ends 328 of the filament extend from the protrusion. Other techniques for attaching filament 326 to protrusion 314 will be readily apparent to those skilled in the art, having read the present patent application. For some applications, filaments 326 are an integral portion of cuff 300, such as when the filaments comprise silicone sutures and the cuff comprises silicone. In order to draw protrusion 314 through hole 312, a surgeon threads filament 326 through hole 312, and draws the filament until head portion 316 passes through the hole. Ends 328 of filament 326 may be coupled to each other in order to make the threading easier to perform. Upon completion of the surgery, the surgeon may clip off the filament. Alternatively, the filament may comprise a biodegradable material, in which case the filament can be left in place to degrade over time. In embodiments of cuff 300 that do not comprise filament 326, the surgeon typically uses standard surgical tools, such as tweezers, to draw protrusion 314 through hole 312.

Fig. 12 is a cross-sectional view of a tubular cuff 400 in a slightly opened position, in accordance with an embodiment of the present invention. Cuff 400 is generally similar to cuff 300, as described hereinabove with reference to Figs. 8-11, except for differences described hereinbelow. Cuff 400 comprises a flap 422 set at an angle _ to the surface of the cuff. The angle _ is typically between 90 and 180 degrees, such as 90 degrees. Optionally, cuff 400 additionally comprises a tab 450, which a surgeon may grasp in order to assist in bringing a hole 412 over a protrusion 414 and holding the hole in place while drawing the protrusion therethrough. Tab 450 typically has a length L of between about 5 and about 25 mm. Cuff 400 typically may be repeatedly opened and closed by the surgeon.

Figs. 13 and 14 are cross-sectional views of tubular cuff 400 in a slightly opened position and a closed position, respectively, in accordance with an

embodiment of the present invention. In this embodiment, cuff 400 additionally comprises a filament 426. The surgeon threads the filament through hole 412, and then grasps the filament while simultaneously moving tab 450 in generally the opposite direction, i.e., in the direction indicated by an arrow 452 in Fig. 13. As a result, protrusion 414 is drawn through hole 412, thereby closing cuff 400 around the tubular tissue.

Fig. 15 is an enlarged schematic pictorial illustration of protrusion 314, in accordance with an embodiment of the present invention. A surface 460 is coupled to cuff 300 in the vicinity of second edge 310, while a surface 462 is oriented towards the second edge, as described hereinabove. Head portion 316 of the protrusion (Figs. 10, 15) typically has a length L1 of between about 0.4 and about 8 mm, a width W1 of between about 0.4 and about 8 mm, and a height H1 of between about 0.4 and about 4 mm. Neck portion 318 of the protrusion typically has a length L2 of between about 0.4 and about 5 mm, a width W2 of between about 0.4 and about 5 mm, and a height H2 of between about 0.4 and about 4 mm. A distance D2 between neck portion 318 and surface 462 is typically between about 0% and about 200% of a distance D1 between neck portion 318 and the surface of head portion 316 opposite surface 462. Alternatively, D1 may be approximately zero.

Reference is made to Fig. 16, which is a schematic, cross-sectional illustration of cuff 300 in the plane B--B of Fig. 9, in accordance with an embodiment of the present invention. Cuff 300 may comprise one or more stimulating and/or sensing electrodes 470, for example using techniques described hereinabove and/or in the patent applications referenced hereinbelow. Alternatively or additionally, cuff 300 may incorporate one or more other features of the electrode assemblies described hereinabove. For example, cuff 300 may comprise one or more internal insulating elements 472 positioned between electrodes 470. The cuff may also comprise one or more end insulating elements 474, which extend towards tubular tissue 476 in order to electrically isolate a portion of tissue 476 within lumen 304 from a portion of tissue 476 outside the cuff.

Cuffs 300 and 400 typically comprise a flexible, resilient biocompatible material, such as silicone or polyurethane. For some applications, the cuffs comprise more than one material, for example, to provide better control of diameters, thicknesses, and/or strengths of various portions of the cuff. For example, an outer wall 478 of cuff 300 (Fig. 16) may comprise a material having a Shore D hardness of between about 40 and about 50, while insulating elements 472 and/or 474 may comprise a material having a Shore D hardness of between about 5 and about 20. Insulating elements 472 and 474 may be somewhat removed from tissue 476 (as shown), or, alternatively, the insulating elements may be disposed in contact or practically in contact with tissue 476. Cuffs 300 and 400 are typically manufactured by extrusion and/or injection molding.

Fig. 17 is an enlarged cross-sectional view of tubular cuff 300 in a closed position, in accordance with an embodiment of the present invention. Shaded area 490 may comprise material having a greater hardness than that of the material of non-shaded areas 492. Alternatively, head portion 316 may comprise a material that is softer than some or all of the material used elsewhere on cuff 300, particularly surrounding hole 312.

Although the techniques described hereinabove with reference to Figs. 15-17 are described with respect to cuff 300, these techniques are also applicable to cuff 400, *mutatis mutandis*.

In an experiment conducted by the inventors, an electrode cuff similar to cuff 400 was implanted around a vagus nerve of a dog. After one month, the cuff showed no signs of tearing or coming loose from the nerve.

As appropriate, techniques described herein are practiced in conjunction with methods and apparatus described in one or more of the following applications which are assigned to the assignee of the present patent application and incorporated herein by reference:

- a US patent application to Gross et al., filed on even date with the present patent application, entitled, "Selective nerve fiber stimulation for treating heart conditions,"

- US Provisional Patent Application 60/383,157 to Ayal et al., filed May 23, 2002, entitled, "Inverse recruitment for autonomic nerve systems,"
- PCT Patent Application PCT / IL02 / 00068 to Cohen et al., filed January 23, 2002, entitled, "Treatment of disorders by unidirectional nerve stimulation,"
- US Patent Application 09/944,913 to Cohen and Gross, filed August 31, 2001, entitled, "Treatment of disorders by unidirectional nerve stimulation,"
- US Patent Application 09/824,682 to Cohen and Ayal, filed April 4, 2001, entitled "Method and apparatus for selective control of nerve fibers," and
- US Patent Application 10/205,475 to Gross et al., filed July 24, 2002, entitled, "Selective nerve fiber stimulation for treating heart conditions."

It will thus be appreciated by persons skilled in the art that the present invention is not limited to what has been particularly shown and described hereinabove. Rather, the scope of the present invention includes both combinations and subcombinations of the various features described hereinabove, as well as variations and modifications thereof that are not in the prior art, which would occur to persons skilled in the art upon reading the foregoing description.